

Caffeine prevents exercise-induced hypoglycemia in trained runners

VINICIUS MULLER REIS WEBER^{1,3} ✉, MARCOS ROBERTO QUEIROGA^{1,3}, ANDRÉ LUIZ KIIHN¹, CARLOS RICARDO MANECK Malfatti¹, JESSICA WOUK⁴, SANDRA AIRES FERREIRA³, LUIZ AUGUSTO DA SILVA²

¹Physical Education Department, Midwest State University of Paraná, Guarapuava, Paraná, Brazil

²Physical Education Department, Guairacá College, Guarapuava, Paraná, Brazil

³Post-graduation of Physical Education UEL/UEM, Londrina, Paraná, Brazil

⁴Post-graduation of Pharmaceutical Science, Midwest State University of Paraná, Guarapuava, Paraná, Brazil

ABSTRACT

The objective of this study was to analyze the physiological, biochemical, and perceptive effects of caffeine intake in marathon runners after a maximal treadmill stress test. The sample comprised randomly selected 12 male athletes of long distance races (42,125 km). The participants performed the maximal stress test twice, after ingesting a placebo and caffeine (dose de 6 mg.kg⁻¹) capsules, using double-blind methodology. Anthropometric parameters, heart rate (HR), blood pressure (BP), and subjective perception of effort (SPE) were evaluated before, during, and after the test. Blood samples for analyses of glucose, lactate (LAC), and triglyceride (TG) levels were also collected at the same time. The maximal stress test was performed on a treadmill, and parameters such as VO₂ max and subjective perception of effort (SPE) were analyzed. Before the trial and caffeine/placebo ingestion, capillary blood was collected by finger puncture for subsequent analyses. Subsequently, the maximal treadmill stress test was initiated with a 3-minute low intensity warm-up phase. The trial continued with the maximal treadmill stress test protocol, followed by a cool-down period (walk) until HR normalization. The athletes remained seated for 10 minutes, and during this period, HR and BP were measured, and blood samples were collected. HR values presented no difference between groups.

✉ **Corresponding author.** Physical Education Department, Midwest State University of Paraná, Guarapuava, Paraná. Simeão Camargo Varela de Sá Street, Vila Carli, 03; Zip code: 85040-080. Brazil.

E-mail: viniciusweber1994@gmail.com

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However, glucose, TG, and LAC levels different after caffeine intake. The results of the present study demonstrated that caffeine ingestion modifies glucose, TG, and LAC availability during exercise in trained runners. **Keywords:** Caffeine; Exercise; Glucose; Heart rate; Exercise test; Biochemical.

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INTRODUCTION

Caffeine is considered an ergogenic substance utilized by athletes during sports practice. In general, a 3 to 6 mg.kg⁻¹ dose of caffeine anhydrous is consumed 30 minutes before physical activity (Goldstein et al., 2010). However, it is important to note that caffeine, when utilized in high dosages and frequency, may cause adverse effects. This unlimited usage may alter the normal functioning of the nervous, digestive, endocrine, and cardiovascular systems, causing dehydration, tachycardia, tremors, palpitation, gastritis, and insomnia (Altermann et al., 2008). Even when caffeine is consumed regularly, it may cause adaptation (tolerance) in the nervous, endocrine, cardiovascular, and muscular systems. Therefore, the individual may feel the need to increase its dosage to notice its effects (Smith, 2002).

Graham (2001), reported that the dosages of caffeine that are regularly utilized in experimental studies ranged from 3 to 9 mg.kg⁻¹. The author also suggested that dosages between 3 and 6 mg.kg⁻¹ are the most adequate.

Caffeine is broadly utilized as an ergogenic strategy (Paluska, 2003). However, the diversity of biochemical interactions between the energy production pathways and caffeine's large metabolic effects complicate the full understanding of the mechanisms of action of caffeine (Doherty and Smith, 2004; Graham et al., 2008). Therefore, it is important to study the effects of caffeine in different sporting situations to clarify its possible benefits in short-duration and long-duration exercises. The effects of caffeine intake in long distance runners are examined to clarify its metabolic and biochemical effects and the duration of its ergogenic action to improve the individual's performance (Vanakoski et al., 1998).

The consumption of a moderate dose of caffeine in progressive and maximal stress tests did not demonstrate significant results, which suggest its inefficiency. Nevertheless, studies that utilized dosages of 10 mg.kg⁻¹ or higher have reported athletes' better performance on exercise tests after caffeine intake (Graham and Spriet, 1996). Caffeine may directly influence in mechanisms involved in the level of performance on endurance exercises. Saving muscle glycogen in the first 15 minutes of physical exercise is essential for good performance, as it aids increase in intramuscular triglycerides. Another effect of caffeine is related to its capability of stimulating potassium transportation to inactive tissues, which decreases potassium plasmatic concentrations and maintains the excitability of the cells during muscular contraction (Lindinger et al., 1993).

Caffeine may also increase GLUT-4 expression due to elevated levels of [Ca²⁺] and increased expression of the AMPK enzyme (Park et al., 2007; Chu et al., 2011). Similarly, caffeine also stimulates the increase of GLUT-4 mRNA in skeletal muscle, increasing the gene transcription of this transporter protein (Egawa et al., 2009). During physical exercise, caffeine mechanisms to stimulate GLUT-4 may be related to the Na⁺/K⁺ pumping activity, intramuscular concentration of Ca²⁺, and increased levels of AMPc enzymes (Nabholz, 2007). All these facts may improve the energy availability to maintain physical exercise.

Further, caffeine intake increases the mobilization of free fatty acids (FFA). This event may occur because there is an increased clearance of catecholamines, which are adenosine receptor antagonists. High levels of fatty acids in blood and muscles accelerate the oxidation of this energetic source, maintaining normal hepatic and muscular glycogen levels. All these facts may improve the performance of athletes during physical activities, increasing exercise time until exhaustion (Graham, 2001; Silveira et al., 2004; Wilmore and Costill, 2001).

The rise in FFA increases citrate concentrations in the cytosol, inhibiting the phosphofructokinase enzyme. High levels of this enzyme promote an increase in the concentrations of phospho-glucose-6 and byphosphato-fructose-1,6, which in turn inhibit the hexokinase enzyme. This enzyme affects the glycolysis process, may impede the utilization of glucose as an active substrate, and promote its storage as muscle glycogen (Randle et al., 1964).

Thus, the objective of this study is to analyze the effects of caffeine intake on physiological, biochemical, and perceptive parameters in marathonists submitted to a maximal stress test.

MATERIALS AND METHODS

Participants

This study was proposed to athletes who were members of the Association of Runners of Guarapuava- PR, in July 2016. The participants were required to be competitors of long-distance races, to be aged above 18 years, and to voluntarily participate in the present experiment. Thus, a sample of 12 runners aged 18 to 40 years old (age: 29.0 ± 2.0 years; weight: 69.5 ± 1.9 kg; height: 176.0 ± 1.7 cm; Body mass index [BMI]: 22.3 ± 0.5 kg/m²; Body fat: $9.9 \pm 1.4\%$) was selected. The athletes trained five times a week, and had experience in running on a treadmill and at least five years of experience in training (6.8 ± 5.5 years). The participants visited the laboratory thrice to participate in the protocols.

In the first appointment, runners were informed about the objectives and procedures of this study and they signed the Informed Consent Form (ICF). The ICF conformed to all ethical precepts presented in Resolution 466 of the National Health Council, dated December 12, 2012. Subsequently, the tests were scheduled on the same day, and the participants reported their body weight to aid the calculation of the dosage of the caffeine and placebo capsules. The capsules were created by a commercial laboratory, with a concentration of 6 mg.kg⁻¹ of caffeine and 6 mg.kg⁻¹ of amide (placebo). The caffeine dosage was determined according to Graham (2001) recommendations. This study was previously approved by the Ethics Committee in Research of Midwest State University (UNICENTRO; protocol n° 58722816.6.0000.0106).

In the second appointment, the capsules with caffeine or placebo were randomly provided to the athletes using the double-blind method, and they were ingested 30 minutes prior to each test. The participants were instructed to not train a day before the trial or ingest food or beverages containing caffeine in the 24 hours prior to the tests.

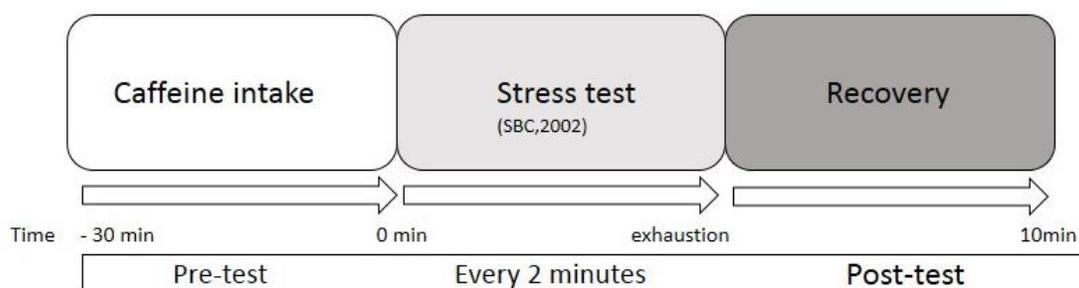


Figure 1. Experimental design

Experimental design

Anthropometric measurements and the maximal stress test were performed with or without caffeine intake. Before and during the effort, hemodynamic parameters and blood samples were collected. A staggered protocol was designed for the maximal treadmill stress test based on the recommendations of the Brazilian Society of Cardiology (SBC, 2002). The participants performed two tests of maximal stress at an interval of a week. Initially, utilizing the double-blind method, participants ingested a caffeine or placebo capsule. After 30 minutes, the athletes initiated the test, which comprised a 3-minute low intensity warm-up of 4 km/h, following which the speed was gradually increased every 2 minutes (stages), until the participants reached parameters of interruption, such as maximum heart rate (MHR) and voluntary exhaustion (Figure 1)

Anthropometric measurements

The second appointment was scheduled seven to ten days after the first. The participants visited the laboratory individually to perform the anthropometric evaluations. The stature was measured with a wooden stadiometer (precision: 0.1 cm). Body mass was determined with a mechanical scale (precision: 100 g; Welmy® SP-BR). Skinfold measurements were performed utilizing a skinfold caliper (Cescorf® RS-BR) in several body regions, such as supraspinale, triceps, subscapular, abdomen, thigh, axilla, and chest. Body density was estimated utilizing multiple regression equations for seven skinfolds, as proposed by Jackson and Pollock (1978). Body fat percentage was determined using the formula recommended by Siri (1961). BMI was defined as the weight in kilograms divided by the square of the height in meters.

Maximal stress test (MST)

In the second and third appointment, participants performed two maximal stress tests, with and without caffeine supplementation. The tests were conducted on an ergometric treadmill ATL® (Inbramed-RS-BR), and it utilized a standardized protocol for assessing maximum staggered effort. Initially, the participants rested for one minute on the treadmill, at an orthostatic position. This was followed by a low-intensity warm-up for 3 minutes, at the speed of 4 km/h. Next, the test was initiated using a protocol that predicted a speed of 7 km/h, with a progressive increment of workload by 1 km/h every 2 minutes. During all tests, verbal encouragements were provided to obtain greater physical effort from the athletes. In addition to voluntary exhaustion, interruption indicators were utilized, such as maximum predicted heart rate according to age ($220 - \text{age}$) and subjective perception of effort (SPE) (10 on the scale).

From the data collected in the maximal stress tests, VO_2 max was calculated utilizing the following formula proposed by the American College of Sports Medicine (ACSM, 2006).

$$VO_2\text{max (ml.kg}^{-1}\text{.min}^{-1}) = (0.2 \times S) + (0.9 \times S \times G) + 3.5 \text{ ml.kg}^{-1}\text{.min}^{-1}$$

VO₂max is the maximal oxygen consumption
S is speed in m.min⁻¹
G is the grade

Hemodynamic and biochemical parameters at rest and during exercise

HR was recorded on a beat-by-beat basis, through a Polar S810 cardiac monitor (Polar Electro Oy, FI-90440, Kempele, Finland). SPE was measured using the Borg CR-10 scale (Borg, 2006). All individuals were familiarized with the scale, and were instructed to incorporate the cardiorespiratory and muscular sensations and to indicate what they felt regarding the physical effort. Parameters such as HT and SPE were collected in the last 15 seconds of each stage (2 minutes). At the end of the maximal stress test, the athletes walked for 3 minutes, at a speed of 5 km/h, with HR monitoring every 2 minutes. The fingertip was sterilized and punched once with a sterile micro lancet (Embramed) and one or two drops of blood were placed directly on

specific strips to analyze the concentrations of glucose, lactate, and triglycerides (Accytrend Plus®, Advantage System, Roche®).

To assess glucose levels, blood was collected to before caffeine/placebo intake, immediately before the test (30 minutes after caffeine/ placebo intake), during the trial (at the 15 last seconds of each stage) and post exercise (at rest during 10'). To analyze the concentrations of lactate and triglycerides, blood collection occurred immediately before the test (30 minutes after caffeine/ placebo intake) and post exercise (at rest during 10').

Statistical analyses

All data were expressed as mean values and standard error of the mean (SEM). Statistical analyses were performed using the SPSS for Windows version 13.0 (Chicago, IL, EUA). First, the Shapiro-Wilk test was used to analyze the normality of the variables, and it was followed by the Student's t-test for paired data. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Table 1 presents the results as mean and SEM for the test variables (average speed and duration of the trial), hemodynamic parameters at rest (HR, systolic arterial pressure [SAP], and diastolic arterial pressure [DAP]), fasting glycemia, and VO_2 max. VO_2 values represent the mean of both maximal stress tests, with and without caffeine supplementation.

Table 1. Sample characterization

Variables	Mean \pm S.E.M.
HRrest (bpm)	71 \pm 3.7
SAP (mmHg)	119 \pm 2.3
DAP (mmHg)	79 \pm 2.4
Glycemia (mg/dL)	95 \pm 3.5
MHR (bpm)	185 \pm 2.8
*Speed (m/min)	290.8 \pm 4.7
Test duration (min)	25.9 \pm 0.6
* VO_{2max} (ml.kg.min ⁻¹)	64.3 \pm 1.0

Mean \pm SEM.; HRrest (heart rate at rest); SAP (systolic arterial pressure); DAP (diastolic arterial pressure); MHR (maximum heart rate obtained at the end of the test); *Mean values of both tests (no significant difference was found).

Figure 2 presents the HR values during and after physical effort. No significant difference was found.

The results for SPE have been shown in Figure 3. No significant difference was found between the caffeine and placebo intake.

Results related to glycemia values have been presented in Figure 4. No difference was found between the participants' who had ingested the placebo and caffeine before the test. However, during the physical test, glycemic values were higher in the caffeine group than were those in the placebo group, at 11', 13', 15', 17', 19', 21', 23', 25', and 27' minutes of effort. After the test (10 minutes), no significant difference was found between the two groups.

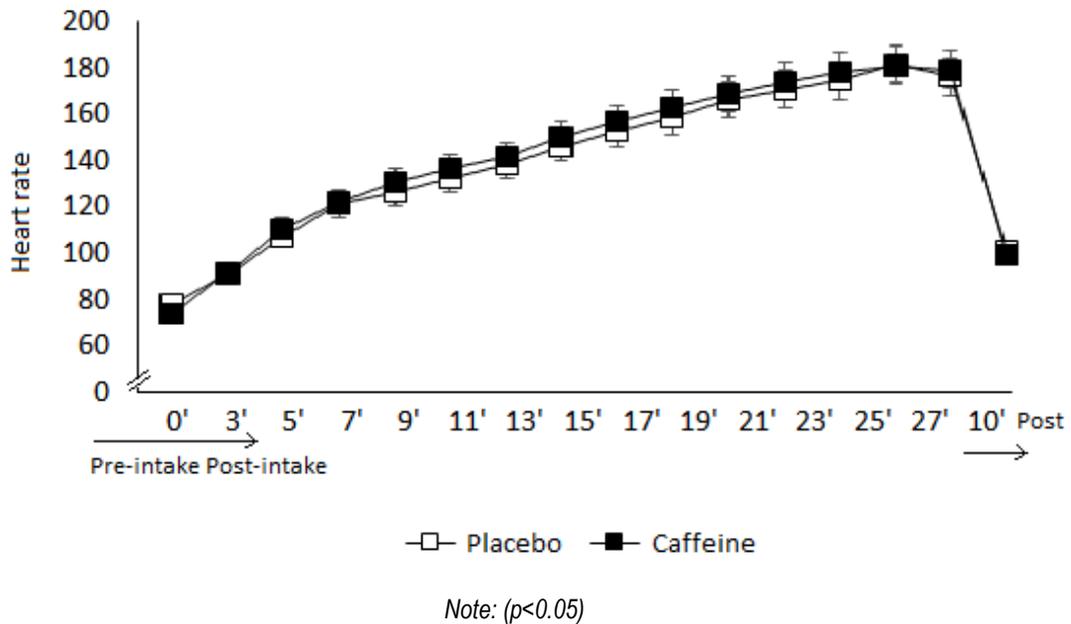


Figure 2. Heart rate (HR) before, during, and after the maximal stress test, with placebo and caffeine intake. Values are expressed as mean values and standard error of the mean (SEM). The Student t-test was employed to compare placebo and caffeine intake

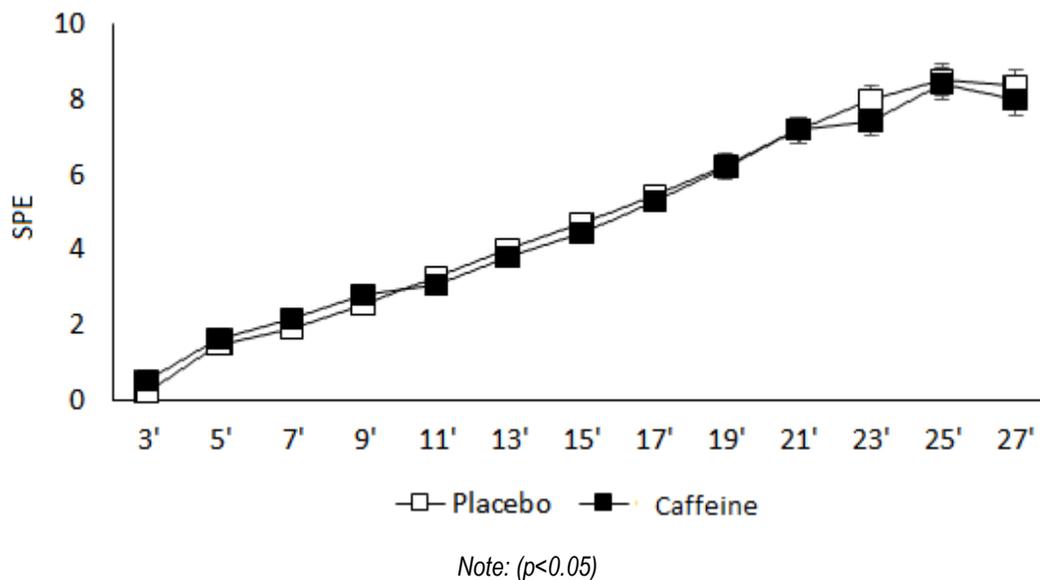
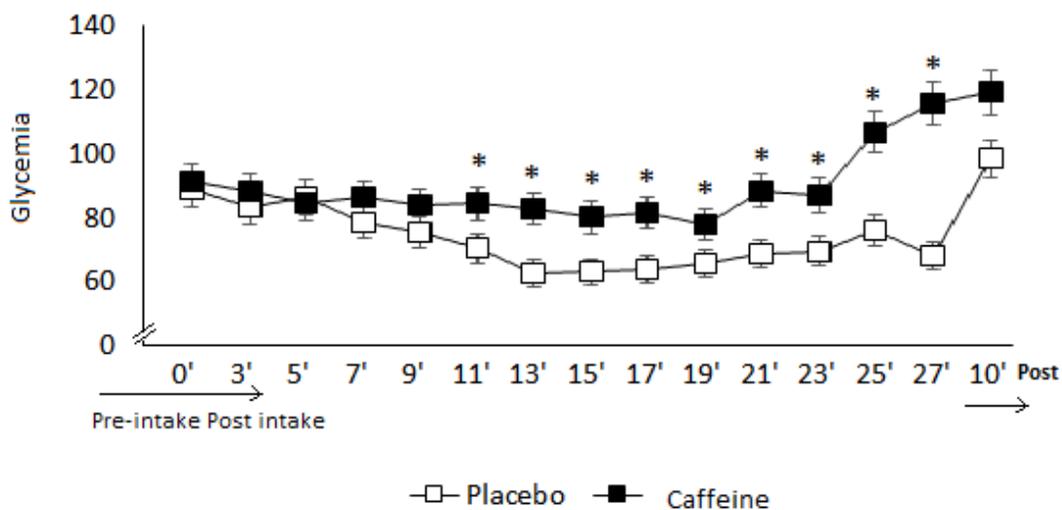
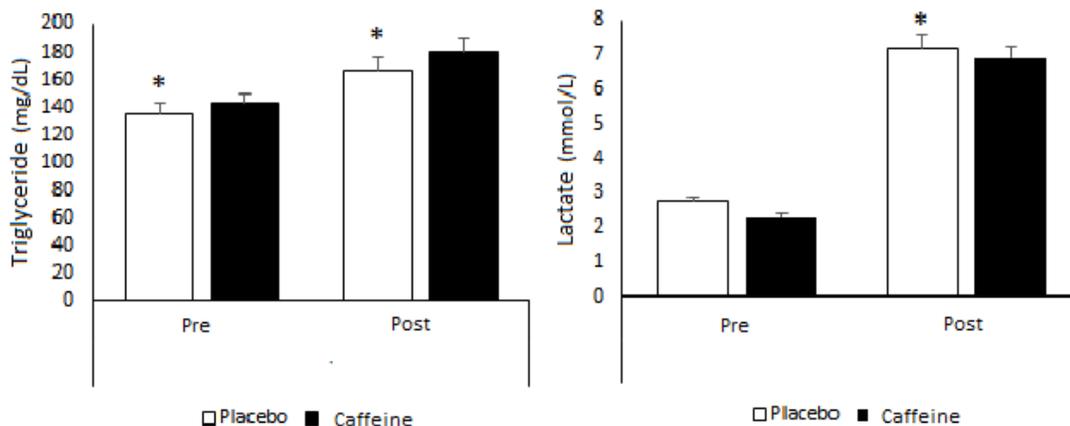


Figure 3. Results of subjective perception of effort (SPE) during maximal stress test with placebo and caffeine intake. Values are expressed as mean values and standard error of the mean (SEM). The Student t-test was employed to compare placebo and caffeine intake



Note: ($p < 0.05$). *Statistical differences ($p < 0.05$) between placebo and caffeine intake

Figure 4. Results of glycemic levels before, during and after maximal stress test with placebo and caffeine intake. Values are expressed as mean values and standard error of the mean (SEM). The Student t-test was employed to compare placebo and caffeine intake



Note: ($p < 0.05$). *Statistical differences ($p < 0.05$) between placebo and caffeine intake.

Figure 5. Triglycerides and lactate values before and after maximal stress test with placebo and caffeine intake. Values are expressed as mean values and standard error of the mean (SEM). The Student t-test was employed to compare placebo and caffeine intake

Triglycerides and lactate values have been shown in Figure 5. Plasmatic triglycerides levels before and after physical effort were higher in the caffeine group as compared to the placebo group. Additionally, plasmatic lactate values were significantly lower after exercise in the caffeine group as compared to the placebo group.

DISCUSSION

The present study demonstrated that caffeine consumption ($6 \text{ mg}\cdot\text{kg}^{-1}$) increased glucose availability, which in turn contributes to better performance of athletes during running races. This finding is relevant to training sessions and long-distance races, in which the athlete needs energy sources to maintain exercise, subsequently reducing the factors associated with fatigue owing to the lack of active substrates.

In the study by Daniels et al. (1998), ten trained cyclists consumed $6 \text{ mg}\cdot\text{kg}^{-1}$ of caffeine and performed exercise on a cycle ergometer ($65\% \text{ VO}_2 \text{ max.}$). No significant difference was found in the HR and BP of the participants. Goldstein et al. (2010) found no difference between these parameters in athletes who consumed caffeine ($6 \text{ mg}\cdot\text{kg}^{-1}$) before an endurance test. In the present study, HR values were not different between the caffeine and placebo intake groups, showing that a dose of $6 \text{ mg}\cdot\text{kg}^{-1}$ of caffeine is not sufficient for modifying cardiovascular and hemodynamic actions.

Yeo et al. (2005) demonstrated the effectiveness of three different treatments in a 120-minute exercise task. The participants ingested a placebo, carbohydrate, or carbohydrate associated with caffeine ($5 \text{ mg}\cdot\text{kg}^{-1}$). Caffeine consumption significantly increased (26%) the oxidation of carbohydrate. However, the levels of glucose did not vary significantly during exercise. Contrary to the findings of the present study, Yeo et al. reported that caffeine was able to increase plasmatic glucose concentrations in sedentary individuals (Yeo et al., 2005). However, their study did not consider the effect of exercise during rest. In Greer et al. (2001) study, the participants who consumed caffeine ($5 \text{ mg}\cdot\text{kg}^{-1}$) demonstrated a significant increase (24%) in the levels of glucose. In the present study, caffeine intake caused an increase of 17% in glucose levels as compared to the placebo. In this regard, evidence suggests that the consumption of caffeine may be associated with metabolic factors, such as gluconeogenesis, during exercise (BOULE et al., 2001).

Caffeine is related to the regulation of glycemic and lipidic metabolism in skeletal muscles. Studies have demonstrated that caffeine consumption might increase the concentration of different glucose transporters (GLUT), such as GLUT-2 and GLUT-4 (Canto et al., 2006; Park et al., 2009). According to some studies, caffeine may stimulate insulin-independent glucose transporters (Wright et al., 2004; Jensen et al., 2007), and may increase the expression of GLUT-4 mRNA and the metabolism of fatty acids (Mukwevho et al., 2008). Caffeine presents metabolic effects similar to 5'-AMP activated protein kinase (AMPK). AMPK has a major role in the regulation of lipidic metabolism and glucose homeostasis. By the simultaneous inhibition of lipogenesis and lipolysis in adipose tissues, the activation of AMPK decreases the circulation of stratified lipids and fat deposits (Long and Zierath, 2006). Additionally, lipid oxidation in the liver and muscles is increased (Ruderman and Saha, 2006), contributing to an improvement in insulin sensibility.

Battram et al. (2006), analyzed the effects of acute ($4.5 \text{ mg}\cdot\text{kg}^{-1}$) and chronic (two weeks) consumption of caffeine on glucose and insulin homeostasis in healthy men (23 ± 0.6 years, 74 ± 1.9 kg). They reported that caffeine consumption significantly increases insulin and C-peptide concentrations, as evidenced by findings of the oral glucose tolerance test (OGTT). However, 90 min after the test, the glucose values were 50% higher in the caffeine group as compared to those in the placebo and decaffeinated groups. After 12 min, glycemic values were controlled, demonstrating no significant differences between groups. Further, glycerol concentration increased with caffeine consumption, 60 min after the test (126 to $154 \text{ }\mu\text{mol/L}$). Caffeine intake also increased epinephrine concentrations at 60, 90, and 120 minutes after the test. Moisey et al. (2008) analyzed healthy men who consumed caffeine ($5 \text{ mg}\cdot\text{kg}^{-1}$) before the OGTT and reported that caffeine intake elevated blood glucose (147%), insulin (29%), and C-peptide (40%) levels as compared to the same in a decaffeinated control group at 60 min after the test.

Triglycerides are essential for long duration and high energetic consumption races because they promote the economical consumption of muscular glycogen and provide energy to the body (9 kcal/g). Thus, athletes' performance improves at the end of the race because of glycogen availability (Ferreira et al., 2003). In the present study, athletes of the caffeine group demonstrated higher levels of triglycerides when compared to the placebo group. This result may be explained by the triglyceride mobilization caused by caffeine.

In contrast, Graham et al. (2008) demonstrated that the increase in triglyceride levels did not alter carbohydrate catabolism. Therefore, the authors suggest that the ergogenic effect of caffeine is not related to the fat and carbohydrate metabolism.

In this study, blood lactate levels were lower in the caffeine group after the test, demonstrating its possible role in the production of adenosine triphosphate (ATP) through the glycolic, anaerobic, and aerobic pathways. In contrast, a study on cyclists demonstrated that plasmatic lactate values were lower in 8, 16, 24, and 32 km trials in the placebo group as compared to those in the caffeine group (6 mg.kg⁻¹) (Skinner et al, 2013). Talanian and Spriet (2016) reported similar lactate values between placebo and caffeine groups until 120 min of moderate intensity exercise. After 120 min, the intensity of training was increased, which provoked a significant rise in blood lactate levels in the caffeine group as compared to that in the placebo group.

CONCLUSION

According to the results of the present study, a supplemental dose of 6 mg.kg⁻¹ of caffeine increased glucose and triglyceride availability and reduced blood lactate concentration in athletes who participated in a staggered protocol maximal stress test. These findings may contribute to strategies focused on increasing the physical performance of athletes by utilizing caffeine as an ergogenic resource.

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COMPETING INTEREST

The authors declare that they have no competing interest.

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